

Breast Implants: Status of Research at the National Institutes of Health (NIH)

Introduction

In compliance with Section 215(a) of the Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250), the NIH has prepared the following report to Congress describing the status of research on breast implants being conducted or supported by the agency.

Breast implants were first marketed in the early 1960s, before the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act required medical devices be shown to be safe and effective. Since 1962, an estimated 1.5 million to 2.5 million U.S. women have had breast implant surgery. Although implants were originally assumed to be biologically inactive and therefore safe, numerous concerns have arisen regarding possible biologic effects. Most of the concern regarding long-term risks has focused on connective tissue disorders given a number of anecdotal reports of these diseases being diagnosed among women with breast implants. In addition, there has been some concern expressed regarding possible effects on cancer risk, particularly breast cancer and cancers associated with immunologic disturbances. In 1992, the U.S. Food and Drug Administration decided to limit the availability of the implants to women who were undergoing breast reconstruction in controlled clinical trials, until the long-term safety of the implants for all women could be established. In addition, Congress charged NIH with conducting a follow-up study to examine the health effects of the implants.

Background

About 80 percent of breast implants in the United States are for cosmetic reasons and 20 percent for breast reconstruction after breast cancer surgery. The majority of previous studies have focused on women who received implants for cosmetic reasons.

1. *Breast Cancer Risk*

A number of previous studies have evaluated the relationship between breast implants and subsequent breast cancer risk. Most have shown that the risk of developing breast cancer is less among women with implants compared to women without implants. In several of the studies, the size of the reduced risk was as much as 50 percent to 60 percent. However, the vast majority of studies did not have enough detailed information on patient characteristics that could affect the development of breast cancer, and had follow-up times of less than 10 years. The most recent studies,

which have been considerably larger than previous studies and have been able to assess long-term risks, do not support the notion that implants are related to breast cancer risk.

2. *Stage at Diagnosis of Breast Cancer*

Some clinical studies have suggested women with breast implants have more advanced breast cancer at diagnosis than women without breast implants. This is because implants have been shown to interfere with the ability to detect breast lesions by mammography. However, several recent epidemiologic studies which compared the stage of disease at breast cancer diagnosis among women with breast implants with other women found no significant differences.

3. *Mortality*

Most of the attention regarding mortality of breast implant patients has focused on breast cancer mortality. These studies have generally shown no differences in breast cancer mortality for breast implant patients as compared with the general population. More recent studies have evaluated other causes of death. Several studies have noted an increased risk of suicide among breast implant patients. No other causes of death have been consistently linked with breast implants.

4. *Types of Implant*

Because earlier reports did not include detailed information about the types of implants, an evaluation of the effect of the implant type on the health risks of the patients has not been possible.

5. *Connective Tissue Disorders*

Anecdotal reports have suggested increased risks of certain connective tissue disorders, including scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. Attempts have been made in a number of epidemiologic studies to assess these relationships. However, given that these are all rare diseases, it has been difficult to draw conclusions regarding whether there are any alterations in risk among breast implant patients. A large meta-analysis that followed an Institute of Medicine review of the literature concluded that there was not sufficient evidence to support any relationships with these disorders.

A recent NCI study emphasized the complexities of evaluating the effects of breast implants on the risk of developing connective tissue disorders (CTDs). Elevated risks associated with self reports of these conditions became statistically insignificant after attempts were made to confirm the

diagnoses through record retrieval and review by board-certified rheumatologists. Further research, including record linkage efforts, utilization of standardized diagnostic criteria for connective tissue disorders, and standardized clinical exams among women with implants, would be needed to understand if a relationship exists between CTDs and breast implants.

6. *Women who Receive Implants for Breast Reconstructive Surgery*

One small study reported no increase in the development of second primary breast cancer in women with silicone implants following mastectomy compared to women who received mastectomies without implants. The small size of the study, however, limits the conclusions. A large study reported in 2004 that women receiving implants after mastectomies for early-stage breast cancer experienced lower breast cancer mortality than women not receiving implants. Assessment of survival among these patients is complex, given unique patient characteristics, disease attributes, and treatment patterns. Interpretation of reduced mortality from breast cancer must be assessed in light of significantly reduced risks of death from most other causes, and the contrasting elevated rates of suicide, which are consistent with findings among women with cosmetic implants.

Note: Any study of the risks of breast cancer or other cancers with women who receive reconstructive implants is more complicated than one involving women with cosmetic implants because it needs to take into account the effects of different breast cancer treatments. A study with breast cancer patients would best be done in the context of a clinical trial where comparisons can be made between women who choose to have reconstruction and those who do not, but who otherwise have received identical treatments.

Current NIH Studies – National Cancer Institute (NCI)

1. Follow-up of Women with Augmentation Mammoplasty

Project Funding Period: October 1, 1992 to present

Project ID: Z01- CP10128 Study #42-92-00

Overview

FY1992 Senate Appropriations Report (102-104) asked NCI to develop a strategy for conducting longitudinal studies of women with various types of

silicone breast implants. In 1993, the NCI's intramural Division of Cancer Etiology (now the Division of Cancer Epidemiology and Genetics) initiated a retrospective cohort study, to assess the long-term health effects of silicone breast implants.

This is one of the longest and largest studies to date on the health effects of breast implants. Most previous investigations have looked at the effects of implants over a shorter time period, typically less than 10 years. Besides the short follow-up periods, previous studies have been too small to evaluate rare diseases. In addition, previous reports have not included information about types of devices implanted or risk factors affecting health, such as medical history, screening practices, and lifestyle behaviors. All of these factors are included in the current NCI study.

Another unique feature of this study is that the investigators compared the breast cancer risks of the implant patients to both the general population and other plastic surgery patients. Previous studies have generally used only the general population for a comparison group, except for a recent Swedish study that compared women with implants to those with breast reduction procedures.

Analyses of cancer risk and overall mortality in this study have been completed and published (See Appendix A). Analyses of the risk of connective tissue diseases related to breast implants are underway.

Participants of the Study

The participants include 13,500 women who had implant surgery for cosmetic reasons in both breasts before 1989. For comparison, about 4,000 women similar in age who had some other type of plastic surgery, such as removal of fat from the abdomen or wrinkles from the face or neck, were identified. All participants were from 18 plastic surgery practices in six geographic areas (Atlanta, GA.; Birmingham, AL.; Charlotte, N.C.; Miami and Orlando, FL.; and Washington, D.C.). The practices were chosen because the plastic surgeons had performed large numbers of cosmetic breast implant surgeries prior to 1989 and were willing to give the investigators access to their records.

Study Design

The medical records from the plastic surgery practices were reviewed to identify patients who were eligible for the study. For eligible patients, trained medical records abstractors collected information about the surgical procedures, the type of implant, any complications, and factors which might affect health status, such as weight or medical history.

Patients were then traced through a variety of sources. Living subjects were asked to complete a mailed questionnaire to collect information about their health

status, including whether they had subsequent plastic surgery as well as lifestyle factors that could affect their health (menstrual, pregnancy, and breast-feeding history, weight, hormone use, cigarette smoking, alcohol consumption, and medical history). Extensive data on the potential short-term (rupture) and longer-term complications (cancer, connective tissue diseases, symptoms of connective tissue disease) were also obtained through the questionnaire.

No clinical examinations were done on the living patients for this study. Attempts were made to verify patient reports of cancer and connective tissue diseases by retrieving medical records from physicians who had diagnosed or treated these diseases. Death certificates were collected for the patients who had died to verify the causes of death.

About 80 percent of the original 13,500 implant patients and 4,000 controls were successfully traced. About 70 percent of those traced as alive completed the questionnaires. These percentages are similar to other comparably designed epidemiological studies.

Results

- NCI researchers found no significant increase in breast cancer incidence or mortality among women with implants compared to controls. In fact, a slight decrease in breast cancer risk was found during the initial 10-year follow-up period, perhaps due to medical screening prior to implant surgery.
- Patients in the study group experienced lower rates for nearly every cancer and for total mortality when compared to the general population, except for an elevation in mortality from brain cancer and suicide. When compared to other plastic surgery patients, implant patients had a slightly higher incidence of cancer, driven primarily by excess risks for brain and lung cancers. Considering the mortality and cancer incidence analyses, and comparison both with the general population and with other plastic surgery patients, excess risks of suicide and cancers of the lung and brain appear to warrant further scrutiny. While the reasons for these excesses are unclear, it is possible that the higher risks observed are due either to chance or to factors common to women who choose to have implants, such as smoking in relation to the lung cancer excesses.
- Researchers at the NCI found no convincing evidence that breast implants have an effect on the development of subsequent connective tissue disorders (CTDs). While a large number of patients reported CTDs, when their records were examined by two board-certified rheumatologists, few cases of the major CTDS (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and Sjogren's syndrome) were considered likely. Further, the small number of confirmed cases of scleroderma and

Sjogren's syndrome made interpretations of the risks difficult. Given the rarity of these two conditions, a study would need to be very large to fully clarify an association.

- The lower overall mortality rates of the implant population support previous findings that people who undergo elective surgery are generally healthier than their peers.

Future Plans

NCI researchers plan to continue to follow the cohort to update the mortality data over time, which may shed light on the observed excess risks of lung and brain cancers, and of suicide. The FDA has studied some of the women in the NCI's study population for implant ruptures.

2. Prophylactic Mastectomy in Hereditary Breast Cancer

Project Funding Period: September 30, 1999 to July 2003
Project ID: R01, CA80181

In a study designed to evaluate the efficacy of prophylactic mastectomy (PM) in preventing breast cancer among high-risk women, investigators at the Mayo Clinic in Rochester, MN are collecting and analyzing data from women with hereditary breast cancer risk who have elected to undergo PM. The Mayo Clinic has served as a referral center for specialized surgeries, including PM, for many years. The investigators have access to two groups of high-risk women who elected PM: unaffected women who have elected PM and women treated for their first breast cancer who elected contralateral PM. For the study, the sisters of women electing PM serve as a reference group.

Although the primary focus of the study is to clarify the magnitude of breast cancer risk reduction for high-risk women who undergo PM, the investigators have also collected clinical information on reconstructive surgery, breast implants, and complications. The additional data about reconstructive surgery and implant use collected by the researchers may provide information about long-term outcomes and effects of implant use in this highly selected group of women.

1. A Convertible PET Camera for Oncology

Project Funding Period: July 1, 1993- August 31, 2003
Project ID: RO1, EB000217

Researchers at the University of Texas are evaluating a positron emission tomography (PET) prototype scanner designed to improve the performance and lower the cost of PET for clinical and research applications. One of the proposed clinical applications is improved diagnosis of breast cancer in women with implants. Traditional x-ray mammography is not as useful in women with breast implants because the implant shows up on the x-ray as a dense shadow which may hide cancerous tumors. Alternatively, PET imaging could improve images that highlight cancerous breast tumors, particularly in women with implants. In addition, the prototype PET scanner may reduce unnecessary biopsy for women with false-positive mammograms. The PET scanner prototype has convertible modes of operation: (1) A high sensitivity brain and animal mode, (2) a whole-body tumor localization mode and (3) a breast mode with 8 times the sensitivity of standard PET scanners. The high-resolution, high-sensitivity brain mode would be useful for detecting small lesions, for a more sensitive differentiation of recurring tumors from necrosis, and for studies of small structures in the brain. The whole-body mode would be useful for tumor localization, cancer staging, and cardiac functional studies. The breast mode, with 8 times the detection sensitivity, can improve the specificity and sensitivity of breast cancer diagnosis. It is also useful for diagnosing small or early breast tumors, especially in younger, high-risk women and women with breast implants, which present difficulties for x-ray mammography.

Current NIH Studies – National Institute of Environmental Health Sciences
(NIEHS)

NIEHS continued support for a project that was initiated in the Food & Drug Administration. This project has been overseen by the FDA Research in Human Subjects Committee and was assigned the FDA designation of Center for Biologics Evaluation and Research protocol #119. The title of the protocol is "EPIDEMIOLOGIC, IMMUNOLOGIC AND IMMUNOGENETIC FACTORS IN SILICONE-ASSOCIATED CONNECTIVE TISSUE DISEASES". This is a case control evaluation of the signs, symptoms, serology and genetic risk factors associated with the development of myositis in women who have had silicone implants or injections. The investigators have enrolled a total of 231 subjects into this protocol. The study, now complete, showed the following result: Women in whom inflammatory myopathy develops after they receive silicone implants constitute an immunogenetically distinct group of patients with myositis. These and other data suggest that autoimmune diseases as now defined may consist of multiple distinct entities, each of which is characterized by different genes and environmental exposures.

APPENDIX A

Publications

Brinton LA, Brown LS, Colton T, Burich MC, Lubin J. Mortality among Augmentation Mammoplasty Patients. *Epidemiology* May 2001; 12 (3): 321.

Brinton LA, Brown LS, Colton T, Burich MC, Lubin J, Hoover RN. Cancer Risk at Sites Other than the Breast Following Augmentation Mammoplasty. *Annals of Epidemiology* May 2001; 11 (4): 248-256.

Brinton LA, Brown LS, Colton T, Burich MC, Lubin J, Hoover RN. Breast Cancer Following Augmentation Mammoplasty (United States). *Cancer Causes and Control* 2000; Vol. 11(9): 819-827.

Brinton LA, Brown LS, Colton T, Burich MC, Lubin J. Characteristics of a Population of Women with Breast Implants Compared with Women Seeking Other Types of Plastic Surgery. *Plastic and Reconstructive Surgery* 2000; 105(3): 919-27.

Brinton LA, Buckley LM, Dvorkina O, Jay H. Lubin, Theodore Colton, Mary Cay Murray, and Robert N. Hoover. Risk of Connective Tissue Disorders among Breast Implant Patients. *American Journal of Epidemiology* Copyright 2004; 60 (7): 620-627.